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REVIEW

Novel nutraceutic therapies for the treatment of metabolic syndrome

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Abstract

Nutraceutic therapies such as berberine, bitter melon, *Gymnema sylvestre*, *Irvingia gabonensis*, resveratrol and ursolic acid have been shown to help control metabolic syndrome (MetS). The effect of berberine on glucose and lipid metabolism, hypertension, obesity and MetS has been evaluated in animal models and humans. Most clinical trials involving bitter melon have been conducted to evaluate its effect on glucose metabolism; nevertheless, some studies have reported favorable effects on lipids and blood pressure although there is little information about its effect on body weight. *Gymnema sylvestre* helps to decrease body weight and blood sugar levels; however, there is limited information on dyslipidemia and hypertension. Clinical trials of *Irvingia gabonensis* have shown important effects decreasing glucose and cholesterol concentrations as well decreasing body weight. Resveratrol acts through different mechanisms to decrease blood pressure, lipids, glucose and weight, showing its effects on the population with MetS. Finally, there is evidence of positive effects with ursolic acid in *in vitro* and *in vivo* studies on glucose and lipid metabolism and on body weight and visceral fat. Therefore, a review of the beneficial effects and limitations of the above-mentioned nutraceutic therapies is presented.

Key words: Nutraceutics; Metabolic syndrome; Berberine; Bitter melon; *Gymnema silvestre*; *Irvingia gabonensis*; Resveratrol; Ursolic acid

Core tip: Metabolic syndrome (MetS) is a cluster of endocrine problems including obesity, dysglycemia, dyslipidemia, and hypertension. Unfortunately, there is no unique treatment to control it. Nutraceutic therapies such as berberine, bitter melon, *Gymnema sylvestre*, *Irvingia gabonensis*, resveratrol and ursolic acid have demonstrated some improvement in anthropometric parameters and cardiometabolic risk factors and could

be considered as treatment for patients with MetS. This review attempts to demonstrate the beneficial effects and limitations of some of these novel nutraceutic therapies.

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INTRODUCTION

Metabolic syndrome (MetS) is a cluster of endocrine disturbances including typically obesity, dysglycemia, dyslipidemia, and hypertension, predisposing individuals to increased risk for atherosclerosis, cardiovascular events, and eventually type 2 diabetes mellitus (T2DM)[1]. However, a number of other parameters that appear to be related to MetS, including non-alcoholic fatty liver disease, should be evaluated in some specific cases to help determine the risk of complications[2,3]. Prevalence of MetS is increasing significantly and is becoming a worldwide health problem[4]. Unfortunately, there is no a single treatment to control MetS; frequently, the option is to treat each component separately. Therefore, any substance that helps to control all the characteristic disturbances of MetS must be considered and studied in depth[5]. Nutraceutic therapies such as berberine, bitter melon, *Gymnema sylvestre* (*G. sylvestre*), *Irvingia gabonensis* (*I. gabonensis*), resveratrol and ursolic acid, which are currently being studied in our Research Institute, among many therapies, have demonstrated to improve some anthropometric parameters and cardiometabolic risk factors. In this regard, they could be considered as treatment for patients with MetS. The aim of this review is to show the beneficial effects and limitations of some of these novel nutraceutic therapies.

BERBERINE

Berberine is an isoquinoline quaternary alkaloid (or a 5,6 dihydrodibenzo[*a,g*]quinolizinium derivative) isolated from many medicinal plants such as *Hydrastis canadensis*, *Berberis aristata*, *Coptis chinensis*, *Coptis rhizome*, *Coptis japonica*, *Phellondendron amurense* and *Phellondendron chinense schneid*[6]. Berberine is traditionally used for its supposed antimicrobial effects and as treatment for diabetes in traditional Chinese, Indian and Middle Eastern folk medicine[7] and has definite potential as a drug included in a wide spectrum of clinical applications.

During approximately 500 A.D., Hongjing Tao recorded the anti-diabetes activity of Rhizoma coptidis for the first time in a book entitled "Note of Elite Physicians". In 1988, the hypoglycemic effect of berberine was revealed when berberine was used to treat diarrhea in diabetic patients in China. Since that time, many physicians in China have used berberine as an anti-hyperglycemic agent. There are a substantial number of clinical reports regarding the hypoglycemic action of berberine in Chinese literature reports[8]. A meta-analysis of berberine reported beneficial effects on blood glucose control in the treatment of T2DM patients similar to those obtained with conventional oral antidiabetic treatments[9]. One study confirms that administration of berberine (0.5 g three times/d) at the beginning of each major meal was able to reduce fasting blood glucose as well as postprandial blood glucose in adult patients with newly diagnosed T2DM. Glycated hemoglobin A1c (A1C) level was decreased by 2.0% with berberine treatment, which is comparable to that of metformin. In poorly controlled diabetic patients[8], berberine regulates glucose metabolism possibly through multiple mechanisms and signal pathways such as increasing insulin sensitivity, activating the adenosine monophosphate- (AMP-) activated protein kinase (AMPK) pathway, modulating gut microbiota, inhibiting liver gluconeogenesis, stimulating glycolysis in peripheral tissue cells, promoting intestinal glucagon-like protein-1 secretion, upregulating hepatic low-density lipoprotein receptor mRNA expression, and increasing glucose transporter[10].

The effects of berberine on lipid metabolism have been evaluated in animals and humans. A systematic review and meta-analysis of randomized controlled trials with berberine show that its administration produced a significant reduction in total cholesterol (mean difference -0.61 mmol/L; 95%CI: -0.83 to -0.39), triglycerides (mean difference -0.50 mmol/L; 95%CI: -0.69 to -0.31), and low-density lipoprotein cholesterol (LDL-C) (mean difference -0.65 mmol/L; 95%CI: -0.76 to -0.54) levels, with a remarkable increase in high-density lipoprotein cholesterol (HDL-C) (mean difference 0.05 mmol/L; 95%CI: 0.02 to 0.09)[11]. The lipid-lowering effect of berberine appears to be mainly due to stabilization of hepatic LDL receptor (LDL-R) in an extracellular signal-regulated kinase (ERK)-dependent manner and also by increasing transcriptional activity of LDL-R promoter by c-Jun N-terminal kinase (JNK) pathway. Berberine also activates AMPK while blocking the AMPK/ERK pathway, resulting in inhibition of lipid synthesis[7].

Few reports in the literature affirm that berberine is able to decrease blood pressure in humans; however, vasorelaxant effects of berberine have been observed in different rat models[7]. Vasodilatator effect of berberine is the result of its action on both endothelium and vascular smooth muscle. Other mechanisms suggested to be involved in the vasorelaxant effect of berberine are angiotensin-converting enzyme (ACE) inhibitor effect and direct release of nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) from rat aortic rings, α_1-adrenoreceptor antagonistic action in rat and rabbit aorta, potentiation of acetylcholine, activation

of K^+ channels and inhibition of intracellular calcium release, and blocking of L-type calcium channels[7]. A recent study showed that berberine could delay the onset and attenuate the severity of hypertension as well as to ameliorate hypertension-induced renal damage in spontaneously hypertensive rats (SHR). Furthermore, berberine could inhibit the activities of the renin-angiotensin system and pre-inflammatory cytokines such as interleukin (IL)-6, IL-17 and IL-23, which are involved in the pathophysiology of hypertension[12].

Several clinical studies have reported the effect of berberine on obesity indicators such as body weight reduction, waist circumference or body mass index (BMI). A study in 116 patients with T2DM and dyslipidemia showed that berberine (1.0 g daily) compared with placebo for 3 mo decreased body weight from 68.7 ± 11.3 to 66.4 ± 11.8 kg[13]. This effect could be due to an inhibition of adipogenesis that may contribute to the anti-obesity activity of berberine. Since then, it has been shown to suppress adipocyte differentiation and reduce lipid accumulation in (3T3-L1) adipocytes. In cells treated with berberine, expression of several lipogenic genes including peroxisome proliferator-activated receptor gamma (PPARγ), enhancer-binding protein alpha (EBPα), sterol regulatory element-binding protein 1 (SREBP-1c), fatty acid synthase, acetyl coenzyme A carboxylase, acyl-CoA synthase, lipoprotein lipase, and cluster of differentiation 36 were all suppressed[8].

The above-mentioned findings show that berberine has excellent potential for prevention and treatment of MetS. A randomized, double-blind, placebo-controlled clinical trial carried out by our research group in 24 patients with a diagnosis of MetS showed that, after berberine administration, patients had a remission of 36% (P = 0.037) in the presence of MetS and a significant decrease in waist circumference in females (106 ± 4 cm *vs* 103 ± 3 cm, $P < 0.05$), systolic blood pressure (123 ± 7 mmHg *vs* 115 ± 9 mmHg, $P < 0.01$), and triglycerides (2.4 ± 0.7 mmol/L *vs* 1.4 ± 0.5 mmol/L, $P < 0.01$) in female and male patients[14].

There is no effective dose for berberine; however, the therapeutic dosage for most clinical situations is 0.2-1.5 g/d for the treatment of various diseases, especially for T2DM[7].

Berberine has been shown to be safe in the majority of clinical trials. In a low percentage of patients, berberine has been reported to cause nausea, vomiting, constipation, hypertension, respiratory failure and paresthesias; however, clinical evidence of such adverse effects is not often reported in the literature[7].

The diverse pharmacological properties exhibited by berberine indicate that the alkaloid has definite potential as a drug in a wide spectrum of clinical applications that include MetS.

BITTER MELON

Bitter melon, also known as *Momordica charantia*, is a common tropical vegetable that has also been used in traditional medicine. The plant grows in tropical areas of Asia, Amazon, East Africa, India and the Caribbean[15]. Approximately 228 different compounds with possible medicinal properties have been isolated from bitter melon fruit, seeds, leaves, pericaps and endosperm. Among these, the most actively studied constituents shown to improve glycemic control include charantin, vicine, momordicin, and polypeptide-p. Polypeptide-p closely resembles bovine insulin with the exception of one extra amino acid, methionine[16].

Several mechanisms of action have been proposed for its effects on glucose, lipids and blood pressure. Studies have shown that bitter melon inhibits the absorption of glucose by inhibiting α-glucosidase, reduces Na^+/K^+-dependent absorption of glucose by the intestinal mucosa and also suppresses disaccharidase activity in the intestine[15,17]. Bitter melon repairs damaged β-cells, stimulates insulin secretion, and enhances insulin sensitivity. Enhancement in insulin sensitivity may be due to multiple factors such as inhibition of protein tyrosine phosphatase 1B (PTP-1B) activity in skeletal muscle, increase in the number and translocation of glucose transporter type 4 (GLUT4) receptors, increase in the rate of phosphorylation of insulin receptor substrate and enhancement in the activity of AMPK. AMPK inhibits cholesterol synthesis in liver by activating 3-hydroxy-3-methylglutaryl-coenzyme reductase. It also stimulates the synthesis and release of thyroid hormones and adiponectin[17]. Other proposed mechanisms for actions include decreased hepatic gluconeogenesis and increased hepatic glycogen synthesis[18]. PPARs are nuclear receptors that control lipid and carbohydrate metabolism. These receptors are regarded as important targets for treating MetS. In animal models, bitter melon upregulated PPARγ- and PPARα-mediated pathways[18].

The hypoglycemic, hypolipidemic and antihypertensive effects of bitter melon have been reported in animal models and clinical trials. Male db/db mice (an animal model of obesity, diabetes, and dyslipidemia) were given sterile tap water as a control or bitter melon daily at a dosage of 150 mg/kg body weight for 5 wk. A1C levels were higher in control mice compared with the bitter melon-treated mice. Additionally, bitter melon reduced PTP-1B activity in skeletal muscle cytosol[19]. Normal and streptozotocin-induced diabetic rats were fed either with basal diet or a diet containing 10% bitter melon powder. Specific activities of intestinal disaccharidases were significantly increased during diabetes. Bitter melon supplementation in the diet clearly indicated amelioration in the activities of maltase and lactase during diabetes[20]. The effect of bitter melon at 10% level in the diet was evaluated in streptozotocin-induced diabetic rats. Amelioration of approximately 30% in fasting blood glucose was observed[21]. The aqueous extract powder of the fruit of bitter melon at a dose of 20 mg/kg body weight was also found to reduce fasting blood glucose by 48% in diabetic rats[22].

To date, most published human clinical trials on bitter melon have focused on blood glucose control. A randomized, double-blind, active-control trial was conducted to assess the efficacy and safety of three doses of bitter melon compared with metformin. Patients were randomized into four groups to receive bitter melon 500 mg/d, 1000 mg/d, and 2000 mg/d or metformin 1000 mg/d. All patients were followed for 4 wk. There was a significant decline in fructosamine in the metformin group (16.8 ± 40.6 μmol/L) and the bitter melon 2000 mg/d group (-10.2 ± 23.3 μmol/L)[23]. After adding bitter melon (800-1600 mg/d) to the current regimens (sulfonylureas and/or metformin) of 42 diabetic patients, fasting plasma glucose was reduced by 26.9 ± 40.8 mg/dL ($P < 0.001$)[24].

The effect of bitter melon on blood pressure and lipids has been evaluated in several experimental studies and only one clinical trial has aimed to investigate its effects on MetS. Acute intravenous administration of bitter melon aqueous extract produced dose-dependent, significant reductions in systemic arterial blood pressure and heart rates of normal and hypertensive Dahl salt-sensitive rats[25]. In another study, normal Sprague Dawley rats were divided into control and three test groups. Rats were administered one of three bitter melon preparations in food for 52 d: Chinese or Indian commercial preparations or an extract of bitter melon. All test groups lowered systolic, but not diastolic, blood pressure. Only the group with the extract significantly lowered ACE activity[26]. The methanol extract of bitter melon fruit was administered to diabetic rats for 30 d. A significant decrease in triglyceride and LDL-C and a significant increase in HDL-C were observed[27]. Bitter melon lowered plasma apolipoprotein B-100 and apolipoprotein B-48 levels in mice fed a high-fat diet and inhibited lipogenesis by downregulating lipogenic gene expression in adipose tissue of diet-induced obese mice[17].

A preliminary open-label, single arm, uncontrolled supplementation trial was carried out in 42 participants to evaluate the effect of bitter melon supplementation (4.8 g/d for 3 mo) on MetS. Decrease in the incidence of MetS rate at the end of the supplementation period was significantly different from that at baseline (19.0%, $P = 0.021$). The difference remained significant for 1 mo after cessation of supplementation ($P = 0.047$). Except for waist circumference (-2.09 cm, $P < 0.05$), the remaining four risk factors of MetS did not show significant decreases after bitter melon supplementation[18].

An effective dose for bitter melon has not been established. In animal models the dose range has oscillated from 20 to 150 mg/kg body weight, whereas in clinical trials the dose has varied from 500 mg to 4800 mg per day[18,19,22,24].

Few side effects have been associated with the use of bitter melon. The most commonly observed adverse effects include mild diarrhea and abdominal pain, which subside after discontinuation. Bitter melon use is also contraindicated during pregnancy because of its abortifacient properties[16].

Although the effect of bitter melon on glucose, blood pressure and lipids has been evaluated in several studies with significant results, only one clinical trial has assessed its effect on waist circumference as a primary outcome. Therefore, its effects on body weight remain to be studied in future clinical trials. The multiple mechanisms behind the hypoglycemic, hypolipidemic and antihypertensive effects of bitter melon and the results reported in previous studies provide a firm base for further well-designed randomized controlled trials to evaluate the efficacy of bitter melon on MetS.

G. SYLVESTRE

G. sylvestre is a medicinal plant belonging to the Asclepiadacea family popularly known as "gurmar" in Hindi, which means "sugar destroying". It is a woody climber that grows in tropical forests in India and South East Asia. Its leaves exhibit a broad range of therapeutic effects due to its active ingredients referred to as gymnemic acids. These are a mixture of at least 17 different saponins, acidic glycosides and anthroquinones[28]. In Indian medicine it is used for its main antidiabetic effects; however, other important metabolic effects have emerged from various studies with potential for treating MetS[29,30].

G. sylvestre helps to promote weight loss possibly through its ability to reduce cravings for sweets and also controls blood sugar levels. Chewing the leaves, rinsing the mouth with aqueous extracts, or topical application to the tongue selectively and reversibly inhibit the sensation of sweetness. Some investigations have suggested that gymnemic acid binds to the receptor located on the taste buds of the tongue and prevents activation by sugar molecules as well as suppressing sugar uptake, presumably by blocking sucrose receptors by one of its molecules, the gurmarin peptide[31,32].

G. sylvestre has also been found to be useful against obesity in accordance with recent preclinical studies in a murine model of obesity where the anti-obesity effect of ethanolic or water-soluble fraction of *G. sylvestre* extract (120 mg/kg, orally for 21 d) was demonstrated in a high-fat diet (HFD)-induced murine model of obesity[33]. Another study with a standardized ethanolic *G. sylvestre* extract (200 mg/kg) administered for 28 d resulted in a significant reduction of BMI, organ weight and visceral fat pad weight, among other metabolic parameters[34]. *G. sylvestre* has also shown a decrease in body weight without rebound on Otsuka Long-Evans Tokushima Fatty rats[35]. Decreasing body weight in humans has been demonstrated in studies using *G. sylvestre* only in combination with various dietary supplements. Therefore, the resulting weight loss cannot be attributed to only *G. sylvestre*[36,37].

Researchers have recently established that *G. sylvestre* does not block only sweet receptors on the taste buds of the mouth. It has the same inhibitory

activity on sodium-dependent glucose transporter 1 found in high levels in brush-border membranes of intestinal epithelial cells[38].

The ability of *G. sylvestre* to lower blood glucose concentrations has been tested as a hypoglycemic agent in combination with insulin in humans, with encouraging results. A preliminary study shows that administration of 200 mg/d of *G. sylvestre* extract decreased the required insulin dose by 50% and lowered A1C in both type 1 and T2DM. It also increased the number of beta cells in the pancreas and therefore the internal production of insulin. When 400 mg/d of this extract is taken with conventional hypoglycemic drugs such as glyburide or tolbutamide, some patients were able to reduce the dose of the drug or even discontinue its use[39,40]. *In vivo* studies with oral administration of an extract of *G. sylvestre*, Om Santal Adivasi (OSA®) (1 g/d for 60 d) induced a significant increase in circulating insulin and C-peptide, which were associated with significant reductions in fasting and postprandial blood glucose. *In vitro* measurements using isolated human islets of Langerhans demonstrated direct stimulatory effects of OSA® on insulin secretion in human cells, consistent with an *in vivo* mode of action through enhancing insulin secretion. As a result, it also stabilizes blood sugar and decreases insulin doses. In fact, one patient with a disease duration of 10 years and another patient with a duration of 2 years and who were both using a total of 20 U of insulin a day were able to completely discontinue insulin at this point in the study[41].

Individual chemical components of extract of *G. sylvestre* have also been shown to be potent and selective antagonists *in vitro* and *in vivo* for the β isoform of liver X receptor[42] in rats in whom *G. sylvestre* was administered at a dose of 200 mg/kg. Significant reductions in lipid levels and an increase in HDL-C have been reported[43].

Compounds from the leaves of *G. sylvestre* may act as an endothelial synthase (eNOS) agonist. To further confirm the results, animal studies were performed with *G. sylvestre* leaves to demonstrate its future usefulness, not only in controlling blood glucose levels in diabetic patients but also to help avoid diabetic complications such as vascular diseases that occur due to decreased availability of NO[44]. One of the most active constituents of *G. sylvestre* is deacyl gymnemic acid (DAGA), which is associated with decreases in homeostasis model asesment (HOMA) insulin resistance, a surrogate marker of insulin resistance, suggesting treatment with DAGA at a dose of 200 mg/kg has beneficial effects on improvement in insulin sensitivity[30]. Conversely, in another study, systolic blood pressure was increased in SHR fed a high sucrose diet, but the clinical importance of this finding is unknown[37].

Clinical studies investigating antidiabetic effects have typically used 200-1000 mg extract daily, standardized to contain 25% gymnemic acids[30,39,41].

Adverse effects have not been reported in long-term studies in patients with type 1 diabetes[45]. However, at high doses, hypoglycemia, weakness, excessive sweating and muscular dystrophy may occur[46]. On the other hand, due to its lipophilic character, *G. sylvestre* may inhibit intestinal absorption of oleic acid[47]. However, the United Nations Organizations has reported only one case of toxic hepatitis due to the use of *G. sylvestre*. Additional studies are needed to support its toxic effect[48]. The above-mentioned evidence supports the possibility of treating MetS with *G. sylvestre*, although more studies are needed.

I. GABONENSIS

I. gabonensis belongs to the family Irvingiaceae. The tree of Irvingia, commonly known as mango bush, wild bush, dikanut or African mango, is native to Central and Occidental Africa[49]. Both the fruit and seeds of *I. gabonensis* are widely consumed in Africa as part of its gastronomy. It has recently been reported that roots, leaves and an extract of the seeds have medicinal properties.

I. gabonensis has been used for the treatment of diarrhea and to shorten the time of lactation in women. It is also administered for the treatment of colicky pain and dysentery. The tree bark has antibiotic properties and helps to heal dermal wounds produced by burning. It has also been administered for the treatment of toothache.

The use of an extract of *I. gabonensis* seeds has been studied as a source of dietary fiber useful to decrease glucose and cholesterol concentrations in diseases such as diabetes mellitus. Gastric emptying is delayed and absorption of glucose at the intestinal level is reduced, leading to better insulin sensitivity in tissues. This extract has also demonstrated to modify distribution of phospholipids, which lowers the plasma concentrations of total cholesterol and triglycerides[50]. Although the use of the extract of *I. gabonensis* has increased, no pharmacokinetic data have been reported.

Different studies have been carried out to determine the composition, antioxidant capacity, mechanism of action and effects of *I. gabonensis.* One study that aimed to identify the principal components of an extract of *I. gabonensis* seeds through high-resolution liquid chromatography coupled to mass spectrophotometry demonstrated that its principal components are ellagic acid, mono-, di-, and tri-O-methyl-ellagic and some long-chain glucosides[51].

In relation to its antioxidant activity, a study was carried out to evaluate the antioxidant capacity of 14 species from Cameroon including *I. gabonensis*. Using different methanol extracts and two different assays to determine antioxidant capacity - the Folin assay and the ferric reduction potential assay - it was found that *I. gabonensis* has an elevated antioxidant concentration of approximately 202 mmol/100 g[52].

Another experimental study was carried out with the aim of investigating the effect of an extract of *I. gabonensis* on inhibition of intracellular triglycerides

and the activity of the enzyme glycerol-3-phosphate in adipocytes 3T3-L1 of a murine model. Expression of some proteins typical of adipogenesis, leptin and adiponectin was also studied. Adipocytes were cultivated for 8 d after initiation of their differentiation and were treated with 0-250 μmol/L of *I. gabonensis* for 12 and 24 h at 37 ℃ in an incubator with humidity at 5%. The results showed that *I. gabonensis* significantly inhibits adipogenesis in adipocytes. This effect appears to be mediated through a decrease in the expression of the PPARγ ($P < 0.05$) and leptin ($P < 0.05$). An increase in adiponectin expression was also found ($P < 0.05$)[53].

An experimental study carried out in diabetic rats fed for 4 wk with a typical rat diet supplemented with *I. gabonensis* or cellulose found that both types of diets significantly reduced glucose, cholesterol and triglycerides concentrations and also increased HDL-C ($P < 0.05$[54].

These results agree with results reported in another experimental study where the potential of a seed extract of *I. gabonensis* was studied to decrease hyperglycemia and hyperlipidemia in a group of diabetic rats administered a diet supplemented with *I. gabonensis* for 4 wk. The results showed a significant decrease in glucose concentrations, food intake, total cholesterol, triglycerides and LDL-C levels. A significant increase in HDL-C was also reported ($P < 0.05$)[49].

A study in which the effect of the administration of a viscous presentation of *I. gabonensis* seeds in diabetic rats was evaluated for 3 wk at a dose of 2 g/kg every 12 h showed that the extract decreased glucose concentrations ($P < 0.05$), decreased activity of the enzymes pyruvate kinase and lactate dehydrogenase ($P < 0.05$) and increased the activity of the enzyme glucose-6-phosphatase ($P < 0.05$) compared with the control group[55].

Another experimental study was carried out to evaluate the long-term effect of an aqueous extract of the bark of *I. gabonensis* administered daily to rabbits for 24 wk. At the end of the study, glucose concentration and body weight significantly decreased ($P < 0.05$)[56].

Some clinical trials have been conducted to determine if *I. gabonensis* has an effect on body weight, glucose and lipid concentrations. A double-blind clinical trial carried out in 40 obese subjects who received *I. gabonensis* or placebo at a dose of 1.05 g three times/d for 1 mo showed that the administration of the extract of *I. gabonensis* decreased on average 5.25 kg of body weight ($P < 0.001$). The subjects also showed a significant decrease of total cholesterol, LDL-C and triglycerides concentrations and increased their HDL-C[57].

Another clinical trial was conducted in 102 overweight or obese subjects who were randomized into two groups: One group who received 150 mg of *I. gabonensis* 30 min prior to breakfast and dinner and the other received placebo at the same dose for 10 wk. The results showed a significant diminution on body weight, fat mass and waist circumference. Significant differences were also found in plasma concentrations of total cholesterol, LDL-C, glucose, C-reactive protein, leptin and a significant increase was shown for adiponectin and HDL-C concentrations in the *I. gabonensis* group *vs* placebo[58].

An approved dose has not yet been established for its use. A systematic review of three randomized controlled trials that evaluated the efficacy of *I. gabonensis* supplementation in the management of overweight and obesity found that the daily dosages differed from approximately 200 mg to approximately 3150 mg[59].

Adverse events reported in some clinical trials regarding the use of *I. gabonensis* are headache, dry mouth, diarrhea, sleep disturbances, and constipation[60]. Acute toxicity studies have not reported any deaths after the 7-d administration of *I. gabonenis* at a dose of 1600 mg/kg in rats[59].

The different studies performed either in animal models or as clinical trials suggest that the administration of *I. gabonensis* may be a promising option for the prevention and treatment of MetS.

RESVERATROL

As a chemical compound, resveratrol (3,5,4-trihydroxystilbene) has been described since the 1940s when it was isolated for the first time from the roots of a white hellebore. Years later, it was extracted from the dried roots of a plant called *Polygonum cuspidatum,* which is often used in traditional Chinese medicine[61].

Today it is known that resveratrol can be found in different quantities in > 70 plants and is also present in some foods and beverages such as nuts, berries, grapes, peanuts and their derivatives such as red wine. The quantity of resveratrol depends of different factors such crop type, geographical origin, and climate[62].

In plants, resveratrol acts as a phytoalexin, a toxic compound produced by plants as a defense mechanism in response to the presence of pests and other stressful situations such as climate.

Resveratrol can be found in two different isomeric forms: *cis* and *trans*, the *cis* form being the more common used form due to its pharmacological properties[63].

Despite the multiple therapeutic effects attributed to resveratrol, its pharmacokinetic characteristics are not favorable because of its poor bioavailability. It is rapidly metabolized and excreted[64].

There is no evidence of the existence of specific receptors for resveratrol. However, resveratrol seems to accumulate in different tissues, mainly related with its absorption and metabolism such as duodenum, colon, liver and kidney[65-67].

Although most of the studies carried out with resveratrol are in regard to its cardioprotective effect, there is evidence that resveratrol has other pharmacological properties in a wide range of chronic diseases such as cancer, T2DM, and degenerative diseases such as Alzheimer's as well as having antithrombotic,

antiosteoporotic and antimicrobial effects[63,67]. Resveratrol acts through different mechanisms. Similar to other polyphenols, resveratrol has an important antioxidant activity and interacts with different receptors, kinases and enzymes[68]. Some studies carried out in *in vivo* models reveal that resveratrol activates sirtuin 1 (SIRT1) and AMPK, both molecules implicated in metabolism regulation; therefore, resveratrol could be a new alternative for the prevention and treatment of MetS[69].

Activation of SIRT1 by resveratrol decreases the activity of PPARγ and therefore adipogenesis, which decreases the number of adipocytes and thus obesity. Resveratrol also increases phosphorylation of the coactivator type 1α of PPAR (PGC-1α) and cyclic adenine monophosphate (cAMP), which increases lipolysis. Resveratrol also enhances the activity of AMPK, which decreases the activity of acetyl CoA carboxylase by its phosphorylation, resulting in a decrease of lipogenesis that contributes to the control of obesity and dyslipidemia. Increase of the activity of AMPK stimulates phosphorylation of the myocyte enhancer factor 2 (MEF2), which results in a higher expression of GLUT4 and therefore a lower resistance to insulin and a diminution of glucose.

Finally, resveratrol increases the activity of endothelial eNOS and therefore the NO concentrations, which contributes to the vasodilation and indirectly to decreased blood pressure[70]. All these effects have been confirmed in different studies, both in animal models and in clinical trials.

A clinical trial was conducted in 11 males with obesity but without any other metabolic alteration. Patients received resveratrol or homologated placebo at a dose of 150 mg/d for 30 d. Results show that resveratrol activated AMPK at the muscular level and increases levels of SIRT1 and PGC-1α, resulting in higher lipolysis of adipose tissue. A decrease in glucose, insulin and HOMA index was also demonstrated[71]. A meta-analysis carried out with 11 clinical trials found that resveratrol administrated at different doses for at least 2 wk in patients with diabetes decreases fasting glucose, insulin, A1C and insulin resistance evaluated through HOMA index, but this meta-analysis did not find any differences in patients without diabetes[72].

Although the information obtained about the effects of resveratrol on cholesterol and triglycerides concentrations is inconclusive, some studies performed in animal models with MetS have shown that resveratrol at different doses reduces atherosclerotic plaque formation, total cholesterol and triglycerides[73,61]. Clinical trials reported in obese patients have not found any significant differences in lipid profile after resveratrol administration[71,74].

Our research group[75] conducted a randomized, double-blind, placebo-controlled clinical trial in 24 patients with a diagnosis of MetS in accordance with the International Diabetes Federation modified criteria. Resveratrol or homologated placebo was administrated for 90 d at a dose of 500 mg three times per day. After resveratrol administration, significant differences were found in total weight (94.4 ± 13.2 kg *vs* 90.5 ± 12.3 kg, $P = 0.007$), BMI (35.6 ± 3.2 kg/m^2 *vs* 34.3 ± 3.0 kg/m^2, $P = 0.006$), fat mass (41.2 ± 7.9 kg *vs* 38.8 ± 6.0 kg, $P = 0.001$), and waist circumference (109 ± 9 cm *vs* 105 ± 10 cm, $P = 0.004$). There were also significant differences in area under the curve (AUC) of insulin (48418 ± 22707 pmol/L *vs* 26473 ± 8273 pmol/L, $P = 0.003$) and total insulin secretion evaluated through insulinogenic index (0.48 ± 0.22 pmol/L *vs* 0.28 ± 0.08 pmol/L, $P = 0.004$).

An approved dose has not yet been established for its use. In a meta-analysis where the effect of resveratrol on glucose control and insulin sensitivity was evaluated, a dose range from 8 to 1500 mg/dL was found[72].

Some adverse effects reported due to the use of resveratrol are headache, abdominal pain and general malaise[75]. At high doses (2000 mg twice daily for 1 wk), a clinical trial reported statistically, but not clinically significant, increased serum bilirubin and potassium concentrations[76]. Daily dosing of 100 mg for 4 wk did not change these values[77].

These results lead to the conclusion that resveratrol could be an option for the treatment of MetS due to the decrease of obesity and by controlling the hypersecretion of insulin characteristic of this group of patients.

URSOLIC ACID

Ursolic acid is a pentacyclic triterpene carboxylic acid present as a free acid or as an aglycone part of saponins[78] and can be obtained naturally or synthetically[79]. It is also known as urson, prunol, micromerol or malol[80]. This compound was considered inactive; however, in recent years interest has been sparked due to the multiple and varied effects of ursolic acid[79,81]. Evidence for this substance appears promising for the treatment of MetS.

The main sources of ursolic acid include components of certain fruits, herbs and plants. Ursolic acid is found in apple peel, cranberry juice and grape skin. It is also found in some common spices like rosemary, thyme and oregano and has been identified in Ayurvedic herbs such as Holy Basil, some traditional Chinese medicinal herbs including Jujuba zizyphus, and in yerba mate and sage. Ursolic acid also is found in some herbs that have attributed antidiabetic effects and is found in small amounts in the leaves of some plants[82,83].

Ursolic acid is formed by 30 carbons distributed in five rings of six carbons and has an hydroxyl group at carbon 3, a carboxyl group at carbon 28 and a double bond at carbon 12 and 13. Its chemical formula is $C_{30}H_{48}O_3$[84]. Some structurally related compounds of ursolic acid include its isomer, oleanolic acid, in addition to corosolic, maslinic, latanolic, pomolic, camarinic and pomolic acids[85]. These compounds share common characteristics of pentacyclic triterpenoids with

apparently similar effects, although differing from each other in strength[85].

Physicochemical properties of ursolic acid give it great stability. Ursolic acid has a molecular weight of 456.70032 g/mol. Its melting point is 269-271 ℃. It has an optical activity of +34° at a concentration of 0.20 g/100 mL in methanol and a molar solubility in pure water at pH 7 and 25 ℃ of 1.11 × 10^{-5} mg/L[80,84].

Evidence demonstrates positive effects *in vitro* and *in vivo* through various mechanisms in glucose and lipid metabolism as well as in body weight and visceral fat usually altered in MetS.

Ursolic acid inhibits the enzyme PTP1B, promoting phosphorylation of the insulin receptor *in vitro*, thereby stimulating glucose uptake[86,87]. PTPB1 is an enzyme associated with the endoplasmic reticulum and plays a key role in signaling metabolic pathways that interacts and dephosphorylates insulin receptor and leptin, causing downregulation signaling of both receptors in modulating the mitogenic actions of insulin[88].

Translocation of GLUT4 is increased by ursolic acid as part of the action on the insulin receptor and manages to improve glucose uptake. GLUT4 is the principal glucose transporter protein and thus plays a key role in regulating whole body glucose homeostasis[88].

Ursolic acid appears to inhibit the α-amylase enzyme, an enzyme that hydrolyzes α-links of large polysaccharides such as starch and glycogen to yield glucose and maltose. Inhibition of α-amylase has been shown to lower blood glucose levels due to lowering the breakdown and absorption of starch[89].

Ursolic acid reduces the activity of aldose reductase and sorbitol dehydrogenase[90,91]. These enzymes catalyze the reduction of hexoses. In the presence of hyperglycemia, aldose reductase converts glucose to sorbitol. The latter is metabolized to fructose by sorbitol dehydrogenase. During this process, the production of sorbitol and fructose occurs. Reduced nicotinamide adenine dinucleotide phosphate is decreased and nicotinamide adenine dinucleotide phosphate is increased[91]. Sorbitol increases intracellular osmotic pressure and damages tissues by cell edema; fructose causes protein fructosylation[90].

The increase in the glyoxalase system produced by ursolic acid represents the decrease of cytotoxicity and chronic complications caused by methylglyoxal, a toxic metabolite produced as a by-product of metabolism. This detoxification reaction is carried out by the glyoxalase system[92].

Administration of ursolic acid was associated with decreased adipocyte differentiation[93]. Adipocytes synthesize and release a wide variety of peptide and non-peptide substances and also store and mobilize triglycerides, cholesterol and retinoids. Lipid-laden adipocytes can be emptied and extended, forming cells that resemble their predecessors not only in appearance but also for its potential for multiplication. This change reflects fully differentiated adipocyte regression to an earlier or less mature, but complete, stage[93].

Overregulation of the c-Cbl associated protein (CAP) was observed in adipocytes treated with ursolic acid[94]. CAP is expressed only in insulin-sensitive tissues (adipose, liver and muscle). Increase in transcription of CAP is directly related to greater sensitivity to insulin in adipocytes. It is postulated that CAP would facilitate phosphorylation of c-Cbl by the insulin receptor, allowing the union of c-Cbl to the insulin-dependent tyrosine kinase. The relationship of CAP is an example of a direct molecular link between PPARγ sensitivity and insulin in adipose tissue[94].

Through the activation of protein kinase A, ursolic acid appears to increase lipolysis *in vitro* as well as to decrease hormone-sensitive lipase and perilipin activity[93]. Lipolysis favors the production of energy from fatty acids into the mitochondria, enabling the generation of free fatty acids from triglycerides stored in adipocytes of white adipose tissue. As a result, there is an activation of fatty acids as well as a translocation to the mitochondria from tissues such as muscle and brown adipose tissue. As a final result, the production of energy occurs from β-oxidation of fatty acids in mitochondria and in some cases in the peroxisome[93].

There is no established dose for ursolic acid. Animal studies have found benefits with ursolic acid at 0.05%-0.2% of the diet[86-93], which is about 10-40 mg/kg based on their weight and food intake. In clinical trials, a 150-mg dose one to three times a day has been used, providing a maximum of 450 mg and revealing some biological activity.

No adverse effects have been associated with ursolic acid in humans. However, studies in animals have reported that ursolic acid at very high doses resulted in a decrease of sperm motility, cell death and DNA damage[95]. Due to the beneficial effects of ursolic acid on several components of the MetS, its clinical administration should be further studied.

CONCLUSION

Nutraceutic therapies such as berberine, bitter melon, *G. sylvestre, I. gabonensis,* resveratrol and ursolic acid have demonstrated substantial scientific information regarding their safety and beneficial effects to be comprehensively considered for treating patients with MetS. Berberine and resveratrol, which already have been studied in patients with MetS, have demonstrated valuable results. For the remainder of the nutraceutics presented in this review, it may be necessary to perform more in-depth studies to be clinically recommended.

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REVIEW

Diabetic foot disease: From the evaluation of the "foot at risk" to the novel diabetic ulcer treatment modalities

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Abstract

The burden of diabetic foot disease (DFD) is expected to increase in the future. The incidence of DFD is still rising due to the high prevalence of DFD predisposing factors. DFD is multifactorial in nature; however most of the diabetic foot amputations are preceded by foot ulceration. Diabetic peripheral neuropathy (DPN) is a major risk factor for foot ulceration. DPN leads to loss of protective sensation resulting in continuous unconscious traumas. Patient education and detection of high risk foot are essential for the prevention of foot ulceration and amputation. Proper assessment of the diabetic foot ulceration and appropriate management ensure better prognosis. Management is based on revascularization procedures, wound debridement, treatment of infection and ulcer offloading. Management and type of dressing applied are tailored according to the type of wound and the foot condition. The scope of this review paper is to describe the diabetic foot syndrome starting from the evaluation of the foot at risk for ulceration, up to the new treatment modalities.

Key words: Diabetes; Diabetic foot; Diabetic ulcer; Diabetic complications; Diabetic neuropathy; Diabetic macroanggiopathy

Core tip: Foot at risk evaluation is crucial to diabetic foot ulceration prevention. Diabetic foot ulcer treatment includes standard wound care procedures, as well as, other novel treatment modalities always as add on therapy.

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INTRODUCTION

The diabetic foot syndrome or disease (DFD) includes several pathologies, mainly diabetic peripheral neuropathy and peripheral arterial disease which result in foot ulceration. Diabetic foot ulceration may ultimately lead to amputation, especially when wound infection or osteomyelitis are involved. Diabetic foot ulcer is defined as a full-thickness wound which is present at a level distal to the ankle in patients with diabetes[1,2]. Special categories like Charcot neuroarthropathy are also included in the DFD[3]. Patients with diabetic foot are also more likely to present with other diabetes-related complications such as nephropathy, retinopathy, ischemic heart disease and cerebrovascular disease[4].

DFD is a common complication which is multifactorial in nature. A good understanding of its various predisposing risk factors would help in both prevention and treatment of this devastating medical condition. The present review paper attempts to address the major challenges and barriers for a better approach of the DFD.

EPIDEMIOLOGY

DFD occurs in all types of diabetes showing higher prevalence among males and in patients more than 60 years old[3]. The burden of DFD is expected to rise in the future, giving that the prevalence of its predisposing factors - mainly the diabetic peripheral neuropathy and peripheral limb ischemia are continually increasing[5]. Epidemiological studies for the DFD incidence and prevalence, present various conduction difficulties mostly related to the diagnostic tests used and the population selection[6].

The annual incidence of foot ulceration is estimated to be approximately 1%-4%[7,8], and its prevalence ranges from 4% to 10%, whereas, the lifetime risk for the development of a diabetic foot ulcer in patients with diabetes ranges from 15% to as high as 25%[7,9].

The presence of foot ulceration is considered to be the main precursor of a lower extremity amputation among patients with diabetes[10]. Apart from the diabetic peripheral neuropathy and the peripheral vascular disease, several other risk factors were identified such as, the limited joint mobility, the foot deformities and any previous ulceration or amputation at the same or contralateral limb. Other risk factors are related to the patient's general condition including; impaired visual acuity, older age, chronic renal disease, long duration of diabetes & sustained uncontrolled hyperglycemia[11-14].

DIABETIC NEUROPATHY

According to the International Consensus Group on Neuropathy; the diabetic neuropathy is defined as the detection of manifestations of peripheral nerve dysfunction in people with diabetes, after excluding other possible causes of peripheral neuropathy[15]. It is not an uncommon condition; in fact it is one of the most common long term complications of diabetes and the most common form of neuropathy in many parts of the world.

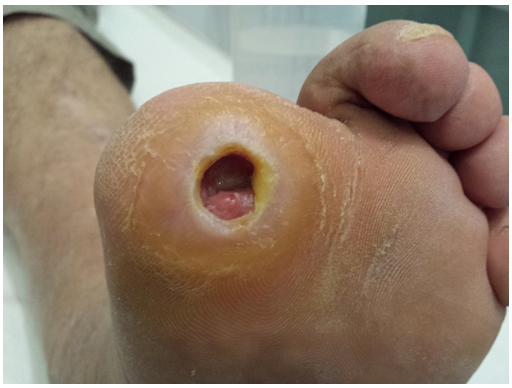

Figure 1 A neuropathic ulcer in a patient with severe diabetic peripheral neuropathy.

The presence of diabetic peripheral neuropathy, even with trivial trauma, is the initiating factor of the development of foot ulceration in patients with diabetes. It has been reported that the risk for diabetic foot ulceration increases by seven fold in patients with peripheral diabetic neuropathy[16,17]. It is also estimated that 45% to 60% of all ulcerations in patients with diabetes are mainly due to neuropathy, while 45% of the ulcers are due to combined neuropathic and ischemic factors (Figure 1)[12,16,18,19].

Distal bilateral symmetrical neuropathy

This form of neuropathy is the commonest presentation among patients with diabetes. It usually starts in the lower limbs while the upper limbs may be also involved too in some cases. It has a progressive course, starting distally and then proceeds proximally as the severity of nerve dysfunction increases. It usually presents in a glove and stocking pattern of abnormal sensations[20].

The distal symmetrical diabetic neuropathy may present with different clinical symptoms. Patients may describe it as symptoms of unpleasant sensations such as tingling, burning, prickling, electric shocks, lancinating pain, hyperalgesia (exaggerated perception of pain on application of a painful stimulus) or even allodynia (contact pain or pain perception due to a non-painful stimulus). Some patients may report abnormal cold or hot feelings in their feet or persistent painful cramp-like sensations even at rest[21]. It is worth mentioning that most of the patients may be completely asymptomatic and unaware of having peripheral neuropathy. Patients may present with diabetic foot ulceration even without any preceding neuropathic complaints[12].

Although the sensory nerve fibers are the most

commonly affected fibers, motor nerve fibers are sometimes affected too, leading to muscle denervation. During the early course of the disease, the muscle power is preserved except mild muscle weakness in the toe extensors. As the disease progresses muscle weakness becomes more generalized affecting small muscles in both feet and hands. This muscle wasting can result in altering the normal foot dynamics and pressure distribution. Wasting and atrophy of small muscles in the foot lead to loss of joint stability and the development of foot deformities. Foot deformities may take several forms such as equinus or varus deformity, hammer toes, cocked-up toes and flat foot changes. These changes lead to pressure distribution disturbance, increased shear stress and friction, ultimately leading in foot ulceration[22-25]. Diabetic peripheral neuropathy is also characterized by the loss of the deep sensation, such as vibration perception and proprioception which in severe cases might lead to sensory ataxia and a positive Romberg's sign. Deep tendon reflexes are usually impaired or lost starting with ankle reflex and progressing proximally to the knee reflex[21].

Additionally diabetic autonomic neuropathy may result in sudomotor dysfunction leading to abnormal sweating and dry skin with cracking and fissuring facilitating the bacterial infection of the foot[26]. Autonomic neuropathy is also associated with thermoregulatory dysfunction and abnormal tissue perfusion. Autonomic neuropathy is also in many cases associated with an unexplained foot edema which is resistant to diuretics. This edema results from shunt opening and hyperkinetic circulation, further adding to the risk of foot ulceration[27].

Diagnosis of the diabetic peripheral neuropathy

Diabetic peripheral neuropathy is diagnosed through careful patient history review and physical examination of the feet. Using the combination of patient's neuropathic symptoms, clinical signs and electrodiagnostic tests would be the best predictor for diabetic peripheral neuropathy[28].

Symptom scores: Various verbal descriptive scales and simple visual analog scales are used in clinical practice to assess and follow up the neuropathic symptoms in response to treatment[29,30]. Symptom scores are used for the evaluation of painful diabetic neuropathy. The most widely used ones are: The Neuropathy Symptom Score (NSS), which is widely used in clinical practice has shown high validity and sensitivity[31-34]. Several other adaptations are also available such as the Neuropathy Symptom Profile, the modified NSS scores of Veves and Young, the Michigan Neuropathy Screening Instrument, and Diabetic NSS[17,35-38].

Semmes-Weinstein monofilament: Semmes-Weinstein monofilament is a widely used tool for the assessment of the diabetic peripheral neuropath in every day clinical practice[39,40]. It assesses the protective ability (evaluates A-beta fibers, determining the patient's threshold for light touch and pressure) of the foot through the application of gentle pressure to the handle until the nylon filament is buckled for 2 s. Many different sizes of filaments are available with the 10-g pressure monofilament (5.07 monofilament) to be the most commonly used for pressure sensation evaluation. Around 90% of the patients with insensate diabetic foot could be identified on testing four planter sites (great toe and the base of first, third and fifth metatarsals)[41]. Monofilament test has shown a sensitivity of (66%-91%) in detection of diabetic patients at high risk for foot ulceration in several studies[18,42,43]. The monofilament test is a quick and painless method, easily acceptable from the patient, easy to administer by the physicians, portable and inexpensive[40].

Vibration perception: The impairment of vibration perception is usually one of the earliest signs of peripheral diabetic neuropathy. Vibration assessment evaluates the large diameter fibers (A-beta fibers). There are several ways for examining the vibration perception threshold (VPT), including: (1) 128 Hz tuning fork: It assesses the vibration perception through application on distal bony prominences of the great toe bilaterally and proceeds proximally on other bony prominences such as the medial malleolus and tibial tuberosity if impairment is noted. Tuning fork gives around 53% sensitivity and there is evidence suggesting that compared to the monofilament test, tuning fork is less predictive for development of foot ulceration[18]; (2) graduated rydel-seiffer tuning fork: The graduated tuning fork depends on optical visual illusion. The fork has 0-8 graded scale, where the examiner can detect the point of vibration impairment or disappearance[44]. Application of the graduated tuning fork detects the presence of vibration perception impairment and the intensity of this impairment. The reduction of vibration perception to less than 4/8 was present in 95% of diabetic foot ulcerations due to peripheral neuropathy[44,45]; (3) neurothesiometer; and (4) biothesiometer.

The neurothesiometer and biothesiometer are electronic devices. They depend on sending vibrations of various strengths through a probe applied to the bony prominence of the great toe. The vibrations are measured in volts per micrometer. As the VPT of the patient increases, the risk for diabetic foot ulceration due to neuropathy increases. A vibration threshold of more than 25 V has been reported to have a sensitivity of 83%. The risk of ulceration in the group of patients with sensitivity between 25 and 33 V was increased by eight times compared to twenty-fold increase associated with values of more than 42 V[46,47].

Nerve conduction studies: Nerve electrophysiologic conduction studies are not routinely used in clinical practice for diagnosis of diabetic neuropathy. They

are objective, non-invasive, highly reliable parametric measures which are useful in monitoring the progression of diabetic peripheral neuropathy especially in asymptomatic patients[48]. They are also extremely useful in atypical presentations of neuropathy and in superimposed forms of mononeuropathies[49]. Electromyography and nerve conduction studies such as NCV and F waves can detect the type of nerve injury, extend, symmetry and severity of the lesion[50].

Other methods of assessment: (1) Nerve biopsy: It is an invasive procedure used for diagnosis of peripheral neuropathy and atypical presentations in patients with diabetes, usually using sural nerve biopsy[51]. Nerve biopsy has many complications such as postoperative pain at the site of nerve biopsy, parasthesia, allodynia and sensory disturbances at the sites of nerve distribution especially in patients with diabetes[52]. Assessment of efficacy of treatment and disease progression can be determined depending on morphological parameters such as axonal atrophy, density of myelinated fibres and axo-glial dysjunction[53,54]; (2) Skin biopsy: It is another less invasive technique alternative to nerve biopsy for studying small nerve fibers using a 3-mm skin biopsy in clinical studies[55]. Several neuronal markers are used to immunostain skin nerves, such asneurone-specific enolase and somatostatin. The best cytoplasmic axonal marker has been proposed is the protein gene product-9.5. Formalin-fixed frozen sections are used in clinical research to visualize and assess the density of intraepidermal nerve fibers[56,57].

Is there a role for validated scores?

Validated scores are available in order to standardize the clinical assessment for the severity of symptoms and the grade of neuropathic impairment. The validated scores include; Neuropathy Disability Score for neuropathic deficits (impairments), NSS for neuropathic symptoms[17] and the Michigan Neuropathy Screening Instrument[36]. According to the Neuropathy Disability Score and the NSS, minimum criteria required for the clinical diagnosis of neuropathy are: (1) the presence of moderate signs of neuropathy in the presence or absence of symptoms; (2) the detection of mild signs in the presence of moderate symptoms.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is one of the multifactorial causes leading to the diabetic foot disease. The presence of PAD alters the normal body response to foot ulcerations and leads to persistent non-healing foot ulcers, when there is an increased need for blood supply. PAD leads to progression of infection, increases tissue break down and insufficient delivery of oxygen, nutrition and antibiotics. All these factors further contribute to a potential foot amputation[58].

PAD shows higher prevalence among patients with diabetes than the general population. PAD among patients with diabetes is characterized by onset at an earlier age, increased severity, a more rapid progression and equal sex distribution[59]. About 20% of patients having symptomatic PAD had diabetes as reported by the Framingham Heart Study[60]. In patients with diabetes, the risk of PAD is increased by advanced age, duration of diabetes, uncontrolled hyperglycemia and the association with diabetic peripheral neuropathy. The presence of diabetes is mostly associated with below knee PAD such as tibial, popliteal and femoral arterial affection, in contrast to more proximal PAD in the aorto-iliofemoral vessels associated with other risk factors such as hypertension and smoking[61].

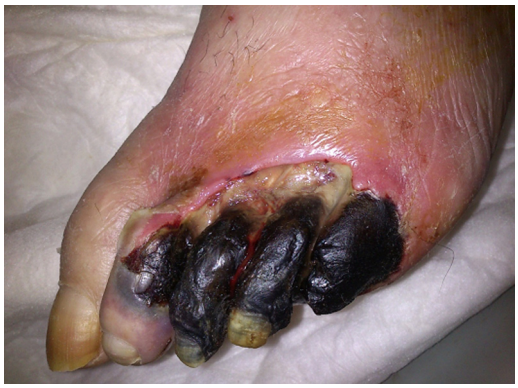

Figure 2 Gangrene in a patient with type 2 diabetes and severe peripheral arterial disease.

PAD is characterized by the presence of intermittent claudication, which is defined as cramping or aching pains usually in the calf muscles, but can also be present in thighs or the buttocks. Intermittent claudication is aggravated by walking exercise that it forces the patient to stop walking and relieved by rest. In severe cases of PAD, pain may be present even at rest, limb may show gangrenous changes, tissue loss; which is known as critical limb ischemia (Figure 2)[62].

Diagnosis of PAD

The ankle-brachial index: The ankle-brachial index (ABI) is a simple bed-side screening tool for the presence of PAD. PAD simply depends on the calculation of the ratio between the systolic pressure of the ankle arteries and the systolic pressure at the brachial arteries[63]. ABI is an inexpensive method that can assess the severity of PAD as it usually correlates with the patient's reported symptoms and functional status. The normal range is of ABI is between 0.9-1.3, falsely elevated values of ABI can result in cases of calcified, non-compressible arteries. Thus the ABI method may lead to underestimation of the severity of the disease in patients with diabetes[64].

The toe-brachial index: The toe-brachial index is calculated similar to the ABI, where the systolic pressure is measured using a small cuff and a Doppler probe.

Measuring the toe-brachial index is helpful especially in cases of ABI values more than 1.30, as the small arteries of the lower limb are less likely to be calcified. A toe-brachial index lower than 0.70 is diagnostic for PAD[65].

Segmental limb pressure assessment and pulse volume recordings: The technique depends on plethysmographic cuffs situated over the brachial arteries and different points on the lower limb. The extent and location of PAD can be detected from segmental systolic pressure assessment using a Doppler probe[66].

Ultrasound velocity spectroscopy and imaging: The normal arterial Doppler velocity shows a triphasic signal. When an arterial obstruction is present proximal to the probe, there is loss of the normal reversed flow component on transforming the waveform associated with decreased amplitude, attenuation of all parts of the spectrum and delayed upstroke[67].

Duplex ultrasound depends on combining the B-mode and the pulsed Doppler ultrasound to assess arterial flow and localized velocity information at stenotic sites. Duplex ultrasonography is widely used nowadays detecting with high sensitivity and specificity the arterial patency and extends of obstruction[68]. Duplex ultrasound has certain limitations mainly difficulty in identifying close multiple separate lesions, some difficulty when assessing infrapopliteal, common and external iliac arteries[69,70].

Transcutaneous oximetry and laser - doppler flowmetry: These techniques are used mainly to assess cutaneous blood flow. Cutaneous blood flow is usually normal until late stages of proximal arterial ischemia of the atherosclerotic type, thus, this type of vascular evaluation is not used in every day practice[64].

Magnetic resonance angiography (MRA)[71,72].

Computed tomographic angiography: CTA is superior to MRA as it can detect the presence of calcification, which is advantageous on planning revascularization strategies. The ACC/AHA guidelines recommend CTA on deciding the revascularization techniques in cases of PAD, offering faster image than MRA[63].

Contrast angiography: Although it is the gold standard for the diagnosis of PAD, is rarely required as a diagnostic tool due to the risks associated with invasive procedures. Computer-enhanced digital subtraction angiography can be useful in patients who present with localized stenosis so as to minimize the amount of contrast material injected and for better image resolution[63].

Diabetic foot ulcers.

CLASSIFICATION

The presence of diabetic foot ulceration is the main leading risk for amputation in patients with diabetes. Proper assessment and classification of a diabetic foot ulcer is an essential part for the management of the diabetic foot. A prompt and adequate ulcer treatment may lead to foot amputation prevention, preserving the life quality of the patient.

Several classifications have been proposed for the categorization of diabetic foot ulcers. The most important ones are described below.

Wagner-Meggitt classification[73]

It is one of the earliest and most widely used classifications. It classifies the diabetic foot ulceration depending on how deep the wound is, includes 6 grades: (1) Grade 0: The skin is intact; (2) Grade 1: Presence of ulcer which is superficial; (3) Grade 2: Presence of ulcer which is deep; (4) Grade 3: Deep ulcer with abscess, bone involvement or osteomyelitis; (5) Grade 4: Gangrene in the forefoot; and (6) Grade 5: Whole foot gangrene.

Wagner-Meggitt classification has shown several disadvantages: (1) cannot address all patterns of diabetic foot ulcerations and infections; (2) the presence of infection is addressed in only one stage, thus, the superficial ulcers if infected or ischemic are not properly categorized in this system; and (3) this system does not properly assess the presence of peripheral ischemia in categorization of foot ulcers.

The university of texas system[73]

It classifies diabetic foot ulcers into 4 grades (0-4) according to their depth, and then stages every grade of them according to the presence or absence of infection and ischemia (A-D).

The University of Texas Classification has been validated and has prognostic advantages as it included both infection and ischemia but showed some difficulty in application in day to day practice.

The SAD classification[74]

This classification grades the diabetic foot ulceration according to five ulcer features (size, depth, sepsis, arteriopathy, and denervation) on a 4-point scale (0-3).

SAD classification differs from the other earlier systems by considering both size of ulcer and the presence of neuropathy. It has been validated by demonstrating differences between baselines variable and clinical outcome. Its major drawback is the complexity in practical use.

The pedis classification[75]

The PEDIS system has been proposed by the International Working Group on the Diabetic Foot. This system grades the wound based on five features: (1) perfusion (arterial blood supply); (2) extent (area of the ulcer); (3)

depth of the wound; (4) presence of infection; and (5) sensation.

***The Infectious Diseases Society of America guidelines*[76]**
These guidelines sub classified the infected diabetic foot into three categories: (1) mild: Involvement is restricted to skin and subcutaneous tissues; (2) moderate: Involvement is more extensive or affecting deeper tissues; and (3) Severe: Diabetic foot ulceration is accompanied by systemic signs of infection or metabolic decompensation.

PRINCIPLES OF DIABETIC FOOT ULCERS MANAGEMENT

Wound debridement

Debridement of diabetic foot ulcers is an important initial step in the management of the wound. Several benefits can result from proper debridement including the removal of the necrotic and non-viable tissues and keeping a healthy granular wound bed. One should be careful on the assessment of the ulcer if ischemia is suspected. A revascularization intervention may be necessary before a debridement is performed. Debridement is also stimulating the release of growth factors to promote advancing healing edges[77,78]. Various methods are used for wound debridement.

Surgical debridement: It is the gold standard method in diabetic foot ulceration. To obtain optimal results, healthy tissue loss should be minimized, foot function should be preserved, and deformities which can precipitate recurrence of ulcers should be prevented. Surgical debridement is typically done for ulcers with large amount of necrotic and non-viable tissues. Debridement is performed using a scalpel blade with the tip pointed in a 45-degree angle or a tissue nipper to remove all necrotic and non-viable tissues until a bleeding healthy base is obtained[79].

Enzymatic debridement: Enzymatic debridement is based on the application of topical agents on the ulcer. These agents are usually applied once daily. Their action is based on the necrotic tissue degradation using proteolytic digestive enzymes such as streptokinases, trypsin, papain, fibrinolysin-DNase, collagenase, papain-urea and streptodornase. Data from clinical studies have shown conflicting results about the efficacy of these topical agents, thus, their additional benefits to standard wound care remains unclear. Putting into consideration the need of long time application, as well as, the high cost, their use is usually limited to slowly soften large eschars or debridement of some decubitus ulcerations in sensate limbs. In order to improve efficacy of these agents, a scalpel blade is applied to crosshatch eschars[80].

Mechanical debridement: Although it is a simple and an inexpensive tool, it can remove both viable and also non-viable tissues leading to pain in sensate foot. The wet gauze dressing is applied to the wound bed and then kept to dry. The necrotic debris embedded in the gauze is mechanically stripped from the wound bed on gauze removal[81].

Biological debridement (Maggot therapy): Recently the use of Maggot therapy has re-emerged showing benefits in necrotic tissue debridement, decreasing bacterial load and stimulation of wound healing. Several studies showed the efficacy of Maggot therapy[82-84].

Other modalities: Ongoing research is evaluating other methods such as low energy ultrasound mist for the debridement of diabetic foot ulcers[84].

Pressure offloading

The pressure offloading relieves abnormal pressure applied to the ulcer promoting the wound healing. Several methods have been applied for offloading including; total contact casting (TCC), short leg walkers, half shoes and felted foam dressings. TCC is based on a well-molded plaster cast, resulting in equal pressure distribution to the whole lower limb. This method is very effective with a good wound healing rate when applied properly and changed at least weekly. Although it is an effective method it has significant disadvantages which may limit their use and the choice of other alternatives. Disadvantages of TCC include; time and skill required to be applied properly, secondary skin irritation and ulceration resulting from the cast applied, and impossible daily assessment of the wound[85,86].

Other alternative to TCC is the Scotch-cast boot with a cast sandal to increase mobility and at the same time ensure ulcer relief from pressure. Commercial devices such as the short leg walker and half shoe are readily available, they are preferred by the patients with a better acceptance, simple, easy to apply and inexpensive. Their major disadvantage is that patients can remove them thus cannot ensure patient's compliance with less significant pressure relieving results compared to the TCC[87].

Felted foam dressings allow a customized pressure relief through a felt-foam pad with an opening over the ulceration through which wound assessment and care can be done. The felted foam is used in combination with half-shoe or surgical shoe and when used properly and changed every 10-14 d, has shown more efficacy compared to half-shoe or short walkers alone[88].

Treatment of infection

The presence of infection is a common finding in diabetic foot ulcers which act as an entry route for pathogens. Infections must be diagnosed and treated promptly and adequately as they may rapidly progress to a limb-threatening condition[78]. Also high levels of bacteria can delay or event prevent wound healing and impede

surgical closure of diabetic ulcers[89].

Diagnosis of diabetic foot ulcer infection: Diagnosis of infection is based initially on clinical signs such as redness, temperature, pain, tenderness, edema and the presence of suspected discharge. On clinical suspicion of infection, properly taken cultures from the wound area may be helpful in proper antibiotic treatment selection. It is important to point out that uninfected ulcers is not necessary to be cultured as the results will only indicate the colonizing flora. The most common pathogens in diabetic foot ulcers are aerobic gram positive cocci and gram negative bacteria. Anaerobic organisms are frequently isolated too[78]. Staphylococcus and streptococci are the most frequently causative agents for non-threatening limb infections while limb-threatening infections are mostly polymicrobial in nature[90].

The use of antibiotics in infected diabetic foot ulcer should be carefully applied, in order to be assured that the patient will receive the appropriate antibiotic therapy, for an adequate period of time, along with wound debridement and drainage[90].

Diabetic foot care

To be able to provide an effective plan for diabetic foot syndrome prevention and treatment, a multidisciplinary team approach is required.

This multidisciplinary team approach includes[10,91]: (1) diabetologist/Endocrinologist to optimize the metabolic control for patients with diabetes; (2) diabetes educator and a qualified nurse: To provide special education and assurance; (3) podiatrist who would guide the patient to prevent diabetic foot lesions and provide appropriate treatment; (4) vascular surgeon to assess the vascularity of the lower limbs and provide interventional management whenever required; (5) orthotist: Help in choosing the appropriate foot wear or custom foot wear to allow adequate pressure distribution and thus rapid wound healing; (6) infection disease specialist: For appropriate choice of antibiotics regimen based on culture results; and (7) nutritionist consultation to help in adequate glycemic control, weight loss and also wound healing.

MODERN WOUND CARE MODALITIES

In the recent years, apart from the standard wound care, new diabetic ulcer treatment modalities have been developed[92,93].

Wound dressings

The ideal wound dressing[94]: (1) should be sterile and does not contaminate the ulcer with foreign particles; (2) should be readily available, easy to use and cost effective; (3) should keep a moist environment for adequate wound healing; (4) should be able to absorb excess exudates from the wound; (5) should not adhere to the wound floor, also should be non-allergic and non-toxic; (6) should be able to protect the wound from microorganisms and also provides mechanical protection; and (7) should maintain adequate tissue gaseous exchange and control wound odor.

Topical agents

Wet to dry dressing (simple saline dressing): Wet to dry dressing is included in standard wound care and is considered a method for mechanical debridement, since it presents a good debriding effect in removal of the necrotic tissue and wound preparation[95]. In order to minimize irritation and discomfort, adequate moistening of the dressings with normal saline is done when treating granulating wound tissues to avoid trauma and bleeding[96].

Local antibacterial agents: Antibacterial agents can be used alone or in combination with other dressings except for dry necrotic ulcers. For effective anaerobic coverage, metronidazole gel is used and maintains a moist environment for wound healing[97,98]. Several antibiotics have effective antibacterial action on topical application such as Neomycin, Gentamycin, and Mupirocin. Silver dressings and polyherbal topical preparations have shown good antibacterial action[99]. For effective antibacterial action against Pseudomonas, other gram-negative bacilli, and beta hemolytic streptococci wound infections Sisomycin and acetic acid can be used. Special precautions should be considered when using povidone iodine solution dressings, iodine has been found to be toxic at high concentrations to bacteria and fungi as well as human cells[100,101].

Tulle dressings: Tulle dressings are used mainly for skin grafts and superficial wounds. They can be safely used in granulating and epithelializing tissues as they are impregnated with paraffin, having low dressing adherence properties[102]. Evidence from several previous studies have shown better and faster re-epithelialization rates compared to dry dressing[102-104].

Hydrogel dressings: Hydrogel dressings are considered the best choice for dry wounds with necrotic eschar. Hydrogels provide fluid and good hydration to dry and slough wounds. Although they are very good at absorbing exudates, they should be avoided in diabetic foot planter ulcers as they may cause maceration of the skin surrounding the wound[105-107].

Polyurethane films: Polyurethane films are transparent films coated with a water-proof adhesive dressing. They provide permeable films allowing diffusion of gases and vapor thus an adequately moist wound environment. They have the advantage of being transparent, thus can monitor the wound progression. They also can be used for low exudates wounds, but they may cause maceration of the skin surrounding the

wound[108].

Polyurethane foam: Polyurethane foam is highly used in diabetic foot ulcers. It can absorb large amounts of exudates in a non-adherent nature thus does not cause wound sloughing or trauma on removal. They maintain moisture environment thus allow proper preparation of wound bed and promotes better wound healing[109].

Alginate dressings: Two forms of alginate dressings are available; calcium alginate and calcium sodium alginate. Alginate dressings can absorb large amounts of exudates up to 20 times their weight as shown by several clinical studies[110].

Honey-impregnated dressings: The anti-inflammatory and anti-microbial actions have been shown *in vitro* studies but further studies are required to support strong evidence *in vivo*[111,112].

Growth factors

Growth factors have shown promising results in diabetic ulcer healing. Growth factors stimulate angiogenesis, cellular proliferation and migration, together with promoting enzymatic production. Several growth factors have been studied including; platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor (TGF)-β, TGF-α and insulin-like growth factor..., *etc.*[113]. A recombinant human (rh)-PDGF dressing is available for diabetic foot lesions when added to conventional[114]. EGF in the form of local injections of rh-EGF showed favorable results in neuropathic *vs* ischemic ulceration[115].

The Food and Drug Administration (FDA) announced some warnings regarding the use of a recombinant human platelet-derived growth factor, which contains becaplermin. In both clinical studies and post marketing users, becaplermin was associated with malignancies distant from the application site. Also increased mortality rate from systemic malignancies was reported on using 3 or more tubes of becaplermin gel. Topical enzymes: Several prepared ointments containing enzymes such as fibrinolysin, collagenase or papain have been used in enzymatic debridement of the sloughy tissues and promoting granulation tissue formation. Papain-urea has shown better enzymatic debridement effect when compared to collagenase[116].

Vacuum-assisted closure: Vacuum-assisted devices have shown efficacy in exudates removal and edema reduction. Ideally a pressure of 125 mmHg can generate a negative topical pressure over the diabetic foot wound. It has the advantage of leaving the wound surface moist. It has several limitations; it is contraindicated in cases of osteomyelitis, ischemia, deep tissues exposure such as tendons, bones and blood vessels, presence of necrotic tissues and fistulas[117]. Vacuum-assisted devices are also effective in promoting closure and wound healing in patients with treated infections and treated osteomyelitis[118,119].

Hyperbaric oxygen therapy, Do we have evidence? A systemic treatment where oxygen is breathed but at a higher pressure than the local atmospheric pressure[120]. HBOT has shown increased healing rates of diabetic foot ulcers, however it still controversial whether it can be used as adjuvant treatment or not[121]. Hyperbaric oxygen therapy (HBOT) have the advantage of reduction of tissue hypoxia, edema, increase angiogenesis and erythrocytes deformability, antimicrobial effects and increase fibroblastic activity[122-124]. HBOT is approved as an adjunctive treatment to be used in chronic non-healing ulcers by the Undersea and Hyperbaric Medical Society[125]. The European Committee for Hyperbaric Medicine has set a type 2 recommendation for the use of HBOT in the management of diabetic foot ulcers including patients with ischemic wounds without a surgically treatable arterial lesion or as a complement after vascular surgery, in presence of non-healing wounds[126].

The role of stem cell therapy in PAD: It is worth mentioning that our skeletal muscles have a regenerative capacity as the have multipotentaial and progenitor cells. In cases of critical limb peripheral arterial disease, the transplantation of progenitor cells- derived from bone marrow- has beneficial effects on angiogenesis and ulcer healing as shown in phase Ⅰ and Ⅱ studies. The role therapeutic angiogenesis is a promising and a safe method for management of PAD and limb salvage[127].

CONCLUSION

Concluding, diabetic foot ulceration is generally preventable. The first step in ulcer prevention is the careful screening for foot problems and detection of patients at high risk. More research is still required to improve the diagnosis of conditions leading to foot ulceration. Diversity in the diagnostic criteria and the lack of cut off hinders the standardization of management plans. Multi-disciplinary team approach is required to effectively manage the different aspects of diabetic foot syndrome. Standard wound care is recommended, while modern treatment modalities have shown some promising results in recent studies.

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